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Review article

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Crosstalk between glomeruli and tubules

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Abstract

Models of kidney injury have classically concentrated on glomeruli as the primary site of injury leading to glomerulosclerosis or on tubules as the primary site of injury leading to tubulointerstitial fibrosis. However, current evidence on the mechanisms of progression of chronic kidney disease indicates that a complex interplay between glomeruli and tubules underlies progressive kidney injury. Primary glomerular injury can clearly lead to subsequent tubule injury. For example, damage to the glomerular filtration barrier can expose tubular cells to serum proteins, including complement and cytokines, that would not be present in physiological conditions and can promote the development of tubulointerstitial fibrosis and progressive decline in kidney function. In addition, although less well-studied, increasing evidence suggests that tubule injury, whether primary or secondary, can also promote glomerular damage. This feedback from the tubule to the glomerulus might be mediated by changes in the reabsorptive capacity of the tubule, which can affect the glomerular filtration rate, or by mediators released by injured proximal tubular cells that can induce damage in both podocytes and parietal epithelial cells. Examining the crosstalk between the various compartments of the kidney is important for understanding the mechanisms underlying kidney pathology and identifying potential therapeutic interventions.

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Key points

- Primary glomerular injury can lead to the development of subsequent tubule injury that promotes the development of tubulointerstitial fibrosis and a progressive decline in kidney function.
- Serum factors — for example, immunoglobulins, complement proteins and lipids — rather than albumin itself seem to be key mediators of proximal tubule dysfunction associated with high proteinuria.
- Increasing evidence suggests that injurious factors released from injured tubules, or loss of protective factors, can feedback to the glomerulus, where they promote or exacerbate glomerular injury.
- In models of acute kidney injury, glomerulosclerosis is attenuated in atubular glomeruli. This effect might be related to reduced filtration in the atubular glomeruli and less oxidative stress in podocytes.

Introduction

Regardless of the initial injury, scarring can eventually develop in all anatomical elements of the kidney, including the vasculature, tubulointerstitium and glomeruli. Ongoing scarring leading to loss of functioning nephrons eventually results in progressive decline in glomerular filtration rate (GFR), culminating in kidney failure. Tubulointerstitial fibrosis is the best morphological correlate of decreased GFR, across the spectrum of causes of progressive chronic kidney disease (CKD)[1,2]. However, most investigation has focused on the glomerulus as the major culprit perpetuating progression of scarring in the kidney. Classically, interventions in CKD have focused on the vicious cycle of glomerulosclerosis increasing stress on remnant nephrons, then causing progressively more sclerosis[3]. Tubulointerstitial fibrosis has largely been viewed as a consequence of glomerular scarring, reflecting hypoxia downstream from the scarred glomeruli. In addition, proteinuria is a marker of poor prognosis and increased risk of CKD, and has been postulated to mediate scarring by profibrotic and toxic effects on tubules, resulting in scarring[3].

Over the past decade, acute kidney injury (AKI) has been increasingly recognized as a major risk factor for subsequent CKD[4,5], and the most common underlying cause of AKI in hospitalized patients is acute tubular injury (ATI)[6]. This observation has shifted focus to the mechanisms of progressive scarring resulting directly from tubular injury. The links between ATI and progressive scarring in the tubulointerstitium have been extensively studied, focusing on cell-cycle arrest, failure of repair, and activation of interstitial fibroblasts and myofibroblasts, which leads to increased extracellular matrix (ECM) production and scarring[4]. These concepts have now been expanded to examine how injury in any one part of the kidney affects the overall injury response. Crosstalk between different kidney cell types can mediate repair or promote injury and scarring. Unravelling these mechanisms can pave the way for targeted treatments that shift injury responses from scarring and progressive CKD to repair and maintain kidney function. Increasing evidence shows that injury in the kidney tubules can feed back to induce or exacerbate glomerular injury, and animal studies suggest that injured proximal tubules produce specific mediators that induce damage to both podocytes and parietal epithelial cells.

In this Review, we examine how glomerular damage can affect the kidney tubules and promote tubulointerstitial fibrosis, including disruption to the glomerular filtration barrier, whereby the filtrate contains molecules that can induce tubular damage. We also discuss how dysfunction in the tubules can be sensed in the glomerulus, through mechanisms that include tubuloglomerular feedback, and the mediators that might underlie the propagation of tubular injury to the glomerulus, including soluble factors that promote inflammation or oxidative stress.

Glomerulus-to-tubule crosstalk

Increases in GFR (that is, hyperfiltration) have long been associated with induction of proximal tubule hypertrophy[7], which might help to maintain glomerulotubular balance. Accordingly, several genetic studies indicate that the expression of many genes associated with the proximal tubule is influenced by variations in GFR[8,9]. Of note, a genome-wide association study of 1.5 million humans, combined with human kidney expression quantitative trait loci (QTL), methylation QTL and single-cell open chromatin and expression data, indicated that variants associated with estimated GFR localized to open chromatin areas specific for genes expressed in the proximal tubule rather than glomerular or distal nephron cells[8].

Tubule reabsorption of filtered protein

Although controversy remains[10], most studies indicate that, under normal conditions, adult kidneys filter <1 g of albumin per day and that this filtered albumin is effectively reabsorbed by the proximal tubule[11]. The reabsorption in the proximal tubule of a variety of proteins, hormones, enzymes and drugs is mediated primarily by the apical endocytic receptors megalin and cubilin[12]. Megalin binding initiates clathrin-mediated endocytosis, whereas cubilin internalization is primarily dependent on its association with megalin, although megalin-independent internalization of cubilin in the proximal tubule cell can also occur[12]. After internalization into clathrin-coated pits, proteins are ultimately hydrolysed within lysosomes into amino acids that are then reabsorbed by facilitated diffusion back into the circulation via the basolateral membrane[13–15]. Megalin–cubilin-dependent endocytosis is generally considered to be the main pathway for albumin reabsorption in the proximal tubule. Of note, humans with certain cubilin (*CUBN*) variants associated with reduced function develop albuminuria but not kidney disease[16]. An additional pathway for albumin reabsorption involving neonatal Fc receptor-mediated transcytosis has been suggested, whereby albumin internalized by the megalin–cubilin pathway is released from endosomes and transcytosed by the Fc receptor as an intact protein back into the circulation without degradation[11,17]. However, given the evidence indicating the predominance of the megalin–cubilin system[18,19], whether Fc receptor-mediated endocytosis has a substantial role in albumin reabsorption under physiological conditions remains uncertain.

The autosomal-recessive disorder Donnai–Barrow facio-oculo-acoustico-renal syndrome (DBS-FOAR) is caused by loss-of-function variants in the megalin gene (*LRP2*)[20]. In addition to albuminuria and low-molecular-weight proteinuria, which is indicative of decreased proximal tubule absorption, patients with DBS-FOAR also have decreased estimated GFR and develop glomerulosclerosis[20]. Similarly, a mouse model of DBS-FOAR is also characterized by tubule injury even in the face of increased proteinuria. In addition, this mouse model also developed progressive glomerular injury[21]. These human and experimental results suggest that tubule injury can occur even with

decreased proximal tubule megalin-dependent activity. However, whether this proteinuria and glomerulosclerosis is related to abnormalities in megalin expression on podocytes or due to the feedback from tubule damage (discussed below) remains unclear[21].

Potential damage to distal nephron segments by proteinuria

Although the proximal tubule is the major target of proteinuria-induced injury, evidence of proteinuric damage to more distal tubule sites has also been reported. A 2024 single-nucleus RNA sequencing study of a proteinuric mouse model indicated generalized dedifferentiation of thick ascending limb and distal convoluted tubule epithelia[22]. In a rat model of puromycin aminonucleoside-induced nephropathy, increased albumin uptake in the connecting tubule and cortical collecting ducts increased activation of the nuclear factor-κB (NF-κB) pathway, leading to local expression of pro-inflammatory cytokines. Interestingly, albumin uptake in these nephron segments was mediated by 24p3R, the receptor for neutrophil gelatinase-associated lipocalin (NGAL; also known as lipocalin 2)[23,24]. In addition to albumin, the filtrate in nephrotic range non-selective proteinuria includes serine proteases that can cleave the epithelial sodium channel (ENaC), which is predominantly expressed in the distal tubule, and thereby induce sodium accumulation[25–29].

Evidence against direct albuminuria-induced tubule injury

Although albumin administration to cultured proximal tubule cells can increase cytokine expression, overload endosomes and lysosomes, impairing their function, and induce cellular apoptosis[30], whether proteinuria-induced tubule injury is primarily due to the reabsorbed albumin itself, in either experimental animals or in humans, remains controversial. Because studies in cultured cells do not always produce findings that are consistent with what occurs in vivo, all in vitro studies need to be confirmed with in vivo observations in experimental animals or in humans if possible. Minimal change disease, in which albuminuria predominates, does not usually induce substantial tubulointerstitial injury compared with that observed in conditions with non-specific proteinuria, in which a variety of serum components can be detected in the filtrate. In addition to albumin, which has a molecular weight of 66.5 kDa, serum components passing through a damaged glomerular filtration barrier can include immunoglobulins, complement components, α2-macroglobulin, fibrinogen and transferrin, among others (Fig. 1). A 2022 in vitro study used a kidney tubule microphysiological system to study the effect of albumin alone compared with serum. The investigators found that serum, but not albumin alone, induced the transcriptional and epigenomic changes associated with the altered proximal tubule phenotype observed in vivo with high non-specific proteinuria[31]. Perfusion of albumin alone, mimicking minimal change disease, reduced fatty acid oxidation and mitochondrial function, as well as decreasing ion transport compared with unperfused tubules, but did not otherwise injure the proximal tubules. By contrast, exposure to serum also induced secretion of inflammatory cytokines and cell injury. Moreover, cultured proximal tubular cells exposed to large plasma proteins (100–440 kDa) had increased apoptosis mediated by increased

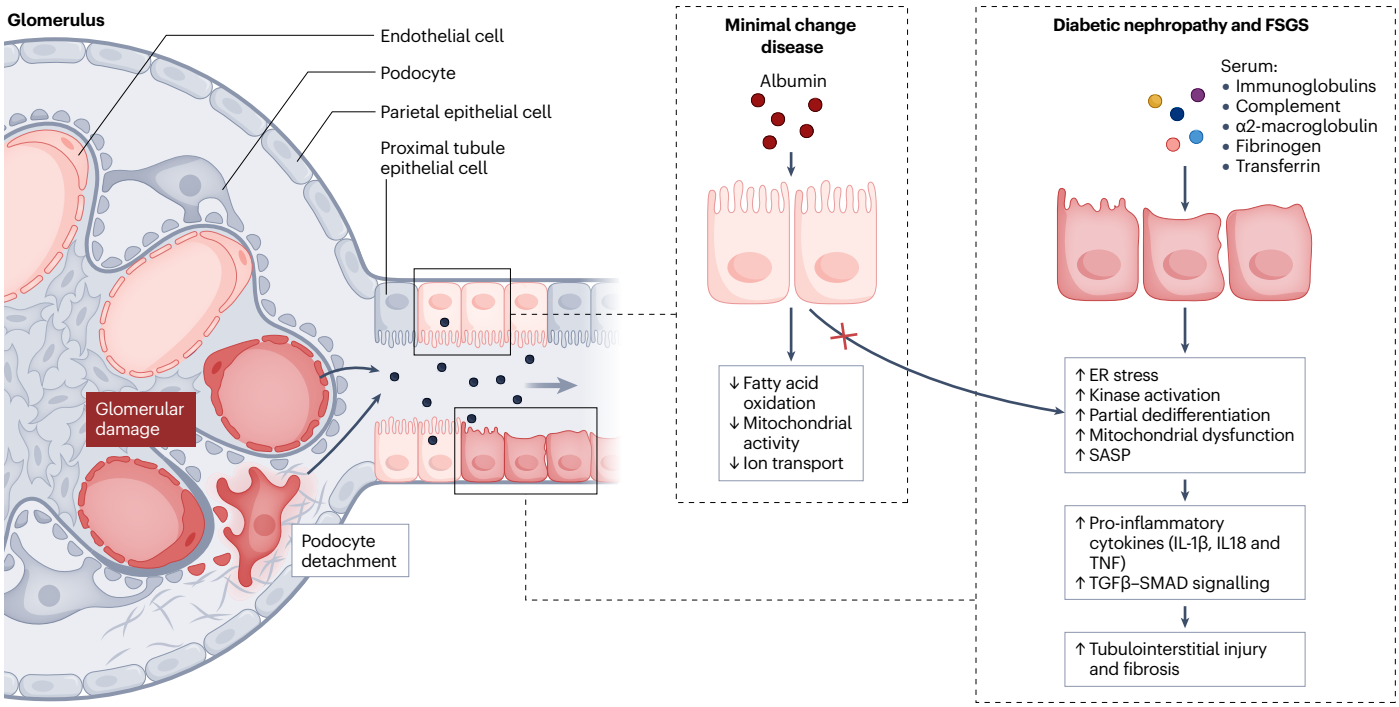

Fig. 1 | Potential mechanisms underlying filtered protein-induced proximal tubule damage. Although exposure of proximal tubule cells to albumin in vitro can increase cytokine expression and induce apoptosis, whether filtered albumin itself can damage proximal tubules remains controversial. In this regard, minimal change disease, characterized by albuminuria, is typically associated with milder proximal tubule dysfunction, inflammatory cytokine production and development of tubulointerstitial injury than other conditions accompanied by non-specific proteinuria. In addition to albumin, serum components passing through a damaged glomerular filtration barrier might include, for example, immunoglobulins, complement components, α2-macroglobulin, fibrinogen and transferrin. ER, endoplasmic reticulum; FSGS, focal segmental glomerulosclerosis; SASP, senescence-associated secretory phenotype; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

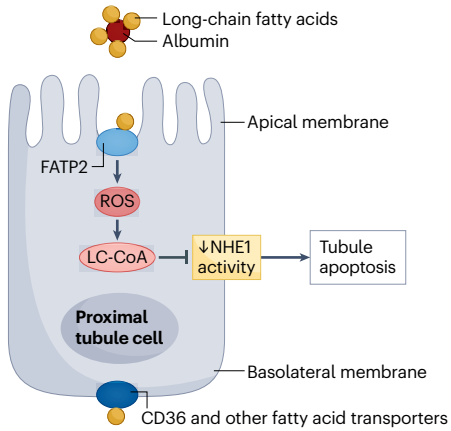

Fig. 2 | Long-chain fatty acids can promote damage in the proximal tubule. Circulating albumin is the main carrier of blood-circulating non-esterified fatty acids, and delipidation of albumin can decrease its toxicity in vitro. Fatty acids bound to albumin enhance the production of reactive oxygen species (ROS), which impairs proximal tubule function and induces dedifferentiation. Moreover, long-chain acyl-CoA (LC-CoA) metabolites inhibit sodium–hydrogen exchanger 1 (NHE1) activity in the proximal tubule, lowering the threshold for apoptosis. In addition to direct injury, non-esterified fatty acids amplify the proximal tubule inflammatory stress response via ROS-induced ATP release. Fatty-acid-binding protein 2 (FATP2; also known as SLC27a), is expressed in proximal tubules and is a major mediator of proximal tubule fatty acid uptake from the glomerular filtrate. Proteinuric diabetic mice with *Slc27a2* deletion have less proximal tubule injury than wild type controls.

Fas and Fas ligand expression compared with cells exposed to smaller plasma proteins. In vivo and in vitro studies indicate that, compared with low-molecular-weight (<100 kDa) proteinuria, high-molecular weight proteinuria was more closely associated with declining kidney function indicated by decreasing estimated creatinine clearance[32,33].

Additional potential inducers of tubule injury

Modified albumin. Clinical evidence suggests a role for modified albumin in mediating CKD progression. In the Chronic Renal Insufficiency Cohort study, increased carbamylated albumin, which might result from alterations in non-enzymatic post-translational modification of the protein, mediated by the urea dissociation product cyanate, correlated with accelerated loss of kidney function[34,35]. In addition to carbamylation, albumin can become glycated in hyperglycaemia, and in vivo and in vitro studies suggest that glycated albumin has a shorter serum half-life than non-glycated albumin and can induce cytokine production in the proximal tubule[15]. Carbamylation, glycation and oxidation of albumin decrease its binding to Fc receptors and might therefore lead to accumulation in lysosomes[17], which might promote proximal tubule dysfunction, as noted above[36]. Increases in both circulating glycated and oxidized albumin have been associated with CKD progression[37].

Filtered lipids. Albumin carries 99% of the non-esterified fatty acids present in blood plasma. Its fatty acid affinity is chain-length dependent, with longer free fatty acids, such as oleic and linoleic acid, having higher binding affinity[38]. Of note, plasma and kidney non-esterified fatty acids, especially long-chain unsaturated free fatty acids, correlate with CKD progression in Pima Indians with type 2 diabetes[39]. Delipidation of albumin decreases its toxicity[40], and proximal tubule metabolism of non-esterified fatty acids induces lipoapoptosis[41,42]. One study showed that long-chain acyl-CoA (LC-CoA) metabolites interact with sodium–hydrogen exchanger 1 (NHE1) in the proximal tubule to promote apoptosis[43]. NHE1 protects against proximal tubule apoptosis by serving as a scaffold for membrane phosphoinositide phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) and its associated cell survival signalling cascades. However, LC-CoA competes with PI(4,5)P2 for binding to the cytoplasmic tail of NHE1, which inhibits NHE1 activity and lowers the threshold for apoptosis[43]. Fatty acids bound to albumin increase production of proximal tubule mitochondrial-dependent reactive oxygen species (ROS), which impairs proximal tubule function and induces dedifferentiation[44]. Interestingly, in cultured proximal tubule cells, fatty acid-bound albumin could also mediate proximal tubule dedifferentiation and increase cytotoxicity, which was not observed with fatty-acid-free albumin[36]. However, uptake of fatty-acid-free albumin can lead to overload of endocytic and degradative pathways[45,46]. Addition of non-esterified fatty acids to cultured proximal tubule cells stimulated mitochondrial ROS-induced ATP secretion through the pannexin 1 channel. ATP induced inflammatory cytokine production via autocrine activation of the P2X7 purinergic receptor, which induced inflammasome activation. This study suggests that in addition to the direct injury, non-esterified fatty acids amplify the proximal tubule inflammatory stress response via ROS-induced ATP release[46].

The fatty-acid-binding protein FATP2 (also known as SLC27A) is not only expressed in hepatocytes but also in proximal tubules, and proteinuric diabetic mice with *Slc27a2* deletion have less proximal tubule injury than wild type controls, suggesting that the uptake of fatty acids by FATP2 might have a role in tubule injury[47–49] (Fig. 2). In addition to FATP2, kidney injury molecule-1 (KIM-1) also mediates proximal tubule fatty-acid uptake, although whether this is a direct or indirect effect remains to be determined[50]. Finally, circulating HDLs, which can be modified by reactive carbonyls such as isolevuglandins and malondialdehyde, can be filtered and taken up by the proximal tubule, where they might induce inflammatory changes and injury[51].

Filtered complement. Evidence suggests a role for the complement system in proximal tubule injury in response to proteinuria. Complement factors are filtered in proteinuric states, and C3 and C5b–9 deposits can be found both in the lumen and within proximal tubule cells. Complement depletion in proteinuric animal models reduced tubulointerstitial injury and confirmed a role for complement in the development of tubulointerstitial disease[52–54]. Studies indicate that the active complement complex C5b–9 induces tubulointerstitial disease only in non-selective proteinuria and not with the selective albuminuria seen with minimal change disease[55,56]. In addition, proximal tubules can produce complement components, and proximal tubule-derived ammonia can activate C3 and initiate alternative complement activation[57]. In addition to C3, the complement factors B, D and I, which can activate C3 through the alternative pathway to form active C3dg, are also produced in the proximal tubule, and increased C3dg can be detected in kidneys of patients with nephrotic syndrome[58,59]. In experimental animals, C3 deposition was also detected on the proximal tubule basolateral membrane, suggesting transcytosis and/or secretion of either reabsorbed or newly synthesized C3 into the tubulointerstitium by the proximal tubule. The proximal tubule also produces C6, and complement-deficient rats that could not form C5b–9 complexes were protected from tubulointerstitial injury after puromycin aminonucleoside-induced proteinuria[54]. Importantly, locally produced C6 is not sufficient to activate the C5b–9 complex

and requires activated C3 (ref. 60). A 2023 study indicates that urinary excretion of C3dg and C5b–9 is associated with proteinuria and the development of pre-eclampsia in pregnant women with type 1 diabetes[61]. In addition, proteinuria in transplant recipients leads to intratubular complement activation with C3dg and C5b–9 deposition[62].

Glomerular-derived cytokines. In addition to the tubule effects of serum proteins or other components filtered through a damaged basement membrane, pro-inflammatory cytokines produced in response to injury to glomerular cells can also be filtered and damage the tubule epithelium. Damage to glomerular endothelial cells was shown to mediate proximal tubule cell damage[63]. Mesangial injury in IgA nephropathy can also exacerbate tubulointerstitial inflammation directly by releasing pro-inflammatory cytokines, as well as indirectly by promoting podocyte damage. Moreover, microRNAs released from damaged podocytes within extracellular vesicles might cause proximal tubule damage[64–67]. By contrast, a 2024 study showed physiological constitutive podocyte secretion of the cold-shock Y-box protein 1 (YBX1), which binds to and inhibits Toll-like receptor 4 signalling, thereby reducing tubular inflammation and injury, consistent with glomerular–tubular crosstalk[68].

Potential mechanisms of proximal tubule injury secondary to glomerular damage

As the above discussion indicates, damage to glomeruli might enable filtration of numerous factors that could injure the tubule epithelium. Single-cell analyses indicate that proximal tubule cells have the greatest differences in gene expression of any intrinsic kidney cell type in response to glomerular injury[69,70]. With excessive proteinuria, the intracellular autophagic degradation pathways involving lysosomes and the endoplasmic reticulum are disrupted and the ensuing endoplasmic reticulum stress prevents complete hydrolysis of the protein burden[71]. Excessive proteinuria also activates kinases in the proximal tubule, including protein kinase C, mitogen-activated protein kinases (MAPKs), c-Jun and Janus kinase (JAK)–signal transducer and activator of transcription (STAT), which can mediate partial dedifferentiation of proximal tubule cells, with increased expression of pro-inflammatory and profibrotic cytokines. Proximal tubule protein overload can induce mitochondrial dysfunction, leading to NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation and increased production of pro-inflammatory cytokines, including IL-1ß, 1L-18, tumour necrosis factor (TNF), IL-6, CC-chemokine ligand 2 (CCL2) and CX3C-chemokine ligand 1 (CX3CL1)[72–74]. These cytokines induce further infiltration and activation of inflammatory cells, amplifying inflammatory cytokine production and tubule injury.

Proteinuria also increases plasma phosphate levels independently of the GFR by decreasing the fibroblast growth factor 23 (FGF23) response, with reduced Klotho expression and increased NaPi-IIa expression[75]. Moreover, excessive proteinuria can activate transforming growth factor-β (TGFβ)–SMAD signalling to promote myofibroblast transformation, leading to hypoxia-inducible factor-1α (HIF1α) activation, which might also have profibrotic effects[76].

Of note, reports suggest that a subset of proximal tubule cells fail to repair after acute injury and persist in chronic progressive kidney disease[77–79]. These injured proximal tubule cells express VCAM1 and CCL2 as well as the transcription factor SOX9 and CDH6, and have a senescence-associated secretory phenotype (SASP)[80,81]. Other investigators have identified a subset of proximal tubule cells producing TGFß and other cytokines that are arrested in a G2/M state[82], although the importance of cell-cycle arrest in mediating the proximal tubule profibrotic phenotype has been questioned[80,83]. Cytokines and chemokines released from the injured proximal tubule mediate macrophage, lymphocyte and basophil influx, and these leukocytes can promote kidney fibrosis[73,78].

Tubule-to-glomerulus crosstalk

Recognition that AKI is a major risk factor for the development of CKD has led to interest in how primary tubular injury can secondarily affect the upstream glomerulus[4,5,84–87]. Even in cases of apparent clinical recovery, the risk of subsequent injury and CKD remains[88].

Tubuloglomerular feedback

Tubuloglomerular feedback regulates GFR through sensing of the intratubular salt concentration and flow by the macula densa cells of the distal tubule, which is connected to its glomerulus of origin at the juxtaglomerular apparatus[10]. When NaCl concentration within the tubular lumen increases, sodium binds to the Na–K–Cl cotransporter 2 (NKCC2) on macula densa cells, resulting in increased intracellular NaCl. The rise in ATP hydrolysis required for reabsorption leads to generation of adenosine, which exits the macula densa and binds to adenosine receptors on the afferent arteriole, inducing vasoconstriction and decreasing glomerular filtration. Conversely, when NaCl concentrations are low, the resulting low intracellular chloride concentration activates neuronal nitric oxide synthase (nNOS), cyclooxygenase 2 (COX2) and microsomal prostaglandin E synthase (mPGES), resulting in increased NO and prostaglandin E_2 (PGE_2) production, which can vasodilate the afferent arteriole[89]. Receptors for PGE_2 — EP2 and EP4 — are present on juxtaglomerular cells, and PGE_2 binding causes release of renin. Renin cleaves angiotensinogen to angiotensin I, and angiotensin-converting enzyme (ACE) then converts angiotensin I into active angiotensin II (AngII), thus activating the renin–angiotensin–aldosterone system (RAAS). Increased AngII causes vasoconstriction of the efferent arteriole and thus increases GFR. In addition, connecting tubuloglomerular feedback activates ENaC in superficial nephron connecting tubules, causing vasodilation of the afferent arteriole and thus increasing glomerular filtration[90].

When the proximal tubules are injured, their reabsorption capacity is impaired, leading to increased solute delivery to the macula densa, and thus decreased GFR via tubuloglomerular feedback mechanisms. However, whether this change has adverse long-term effects on glomerular structure has not been shown directly in humans.

Insights from SGLT2 inhibition. The remarkable renoprotective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors have led to a renewed focus on tubuloglomerular feedback mechanisms[91]. This class of drug was developed with the goal of decreasing hyperglycaemia by promoting glucosuria, while inhibiting sodium reabsorption in the proximal tubules. However, the marked benefits observed on cardiovascular disease, and in both diabetic and non-diabetic kidney disease, were not easily explained by the observed modest decreases in hyperglycaemia. SGLT2 inhibition also decreases adverse glomerular haemodynamics by restoring sodium delivery to the macula densa of the distal tubule, thereby counteracting the activated tubuloglomerular feedback and glomerular hyperfiltration and hypertension that usually prevail in diabetes. However, beneficial effects of SGLT2 inhibition on the progression of CKD were observed, even in patients on RAAS blockade, which also acts to decrease glomerular hypertension. Thus, additional effects of SGLT2 inhibition on proximal tubular metabolism and mitochondrial stress have been proposed and are being actively investigated[92–95].

Of note, the use of animals to clarify potential additional mechanisms of SGLT2 inhibitors has some limitations. An early study reported no benefit for SGLT2 inhibition in the 5/6 nephrectomy rat model, despite this model having robustly mirrored and predicted the beneficial effects of RAAS blockade on the progression of CKD beyond effects on systemic hypertension[96]. In addition, a 2023 study in a mouse Alport model of secondary progressive glomerulosclerosis reported no benefit for SGLT2 inhibition added to standard-of-care ACE inhibition, which again does not reflect the clinical setting[97]. Given these discrepancies, small studies in humans are of great interest. Kidney biopsy samples from 6–10 patients with type 2 diabetes who were treated with SGLT2 inhibitors were compared with samples from patients with diabetes who were not receiving SGLT2 inhibition and healthy individuals[98]. Elegant use of single-cell RNA sequencing demonstrated transcriptional alterations in response to SGLT2 inhibition in all nephron segments, particularly in the distal nephron. Treatment also resulted in decreased transcription of genes associated with glycolysis, gluconeogenesis and tricarboxylic acid cycle pathways in the proximal tubule. By contrast, treatment increased the transcription of those genes in the thick ascending limb compared with levels observed in patients who were not receiving SGLT2 inhibitors.

Mechanistic target of rapamycin complex 1 (mTORC1) has key roles in the response to metabolic, growth- and nutrient-related stress. SGLT2 inhibition decreased tubular mTORC1 signalling towards levels observed in healthy individuals, associated with decreased phosphorylated S6 protein levels in tubules, assessed by immunostaining. These interesting data support the possibility that SGLT2 inhibition might influence metabolic changes in the tubules by decreasing mTORC1 signalling[98]. SGLT2 inhibition might decrease mitochondrial stress by lowering glucose trafficking and its associated metabolic pathways in proximal tubules. How these changes might affect glomerular structural changes remains to be determined. Among patients with diabetes, those treated with SGLT2 inhibition had smaller glomerular volume and a lower increase in mesangial area[98]. Of note, mTORC1 increases have been implicated in podocyte injury in diabetes[99,100], but glomerular cell transcriptional changes were not described in the above human biopsy study[98]. SGLT2 inhibition might also induce sirtuin1 (SIRT1) expression, which could potentially increase erythropoietin levels by stimulating HIF2α[101,102]. Thus, in addition to decreasing adverse glomerular haemodynamics, SGLT2 inhibition might affect nephron metabolism by decreasing hypoxia and its consequent adverse consequences that stimulate secondary glomerular injury.

Proximal tubule injury feedback to exacerbate glomerular injury

The effects of ATI on subsequent glomerular injury have been studied. A transgenic mouse model with tubule-specific diphtheria receptor (DTR) expression (*Six2*-Cre-*lox*P system) allowed selective injury to be induced in the S1 and S2 segments of the proximal tubule[103]. Importantly, recovery was complete and without direct podocyte injury after a single dose of diphtheria toxin. By contrast, inducing injury repeatedly (three times, 1 week apart) caused interstitial capillary rarefaction, interstitial fibrosis and glomerulosclerosis. These in vivo mouse studies demonstrated that isolated proximal tubule injury can result in glomerular injury and that this injury correlated with failed tubular repair, leading to interstitial fibrosis and tubular atrophy. Possible mechanisms include interstitial capillary rarefaction resulting in glomerular ischaemia, or paracrine signalling from the proximal tubule with diffusion from the injured tubule to the adjacent glomerulus. Injured tubules can also have increased backleak (whereby filtrate leaks through the damaged tubular epithelia) owing to loss of E-cadherin and increased apoptosis, further promoting direct communication of injurious mediators to glomeruli via Bowman's space[104,105].

One potential mediator of podocyte dysfunction after ATI is matrix metalloproteinase 7 (MMP7). Wnt–β-catenin signalling increases with kidney injury and promotes fibrosis by upregulating various pathways, including the RAAS, plasminogen activator inhibitor 1 and MMP7. Kidney injury in mice resulting in proteinuria and glomerular injury after chronic angiotensin II infusion or adriamycin was markedly decreased when *Ctnnb1* (encodes β-catenin) was deleted specifically from the tubule[106]. MMP7 could directly affect podocytes by degrading nephrin, a key component of the podocyte slit diaphragm. Exposure to MMP7 in vivo caused proteinuria and, conversely, mice deficient in MMP7 were protected from injury induced by AngII. MMP7 could potentially reach glomeruli directly, as discussed above, or indirectly through the systemic circulation. Exposure of cultured podocytes to conditioned media from proximal tubules injured by hypoxia showed that additional factors can also contribute to podocyte injury, such as arginase II, mediated by increased TGFβ[107].

We established a mouse model of ATI with subsequent podocyte injury after clinical recovery of the tubule injury[108]. In this model, proximal tubular injury was induced by injection of diphtheria toxin in mice that expressed the receptor only in the proximal tubule, under the γ-glutamyl transferase (*Ggt1*) promoter. Injection of diphtheria toxin resulted in AKI with mild tubule injury, with increases in urinary NGAL and KIM1. These animals also expressed human CD25, which is the receptor for the modified *Pseudomonas* exotoxin LMB2, driven by the nephrin promoter (so-called NEP25 mice). After clinical recovery from diphtheria toxin-induced ATI, podocyte injury was induced. Mice with previous ATI had more severe glomerular injury — increased podocyte loss, more severe glomerulosclerosis and more albuminuria — than mice without preceding ATI. When mice were treated with the HIF1 stabilizer dimethyloxalylglycine (3 weeks post-ATI induction), hypoxia decreased and there was less tubular epithelial injury, as well as decreased inflammation and interstitial fibrosis[109]. When podocyte injury was induced 4 weeks later, glomerular injury was less severe than that observed in mice that had not received the HIF1 stabilizer. nNOS was increased after ATI, supporting the hypothesis that abnormal tubuloglomerular feedback could cause a maladaptive rise in glomerular haemodynamics and contribute to worsened podocyte injury[108].

In vitro studies of proximal tubules found that hypoxia or hyperglycaemia could induce the secretion of factors that might reach the glomeruli and promote injury. After hypoxia, cultured proximal tubules secreted more TGFβ1 (ref. 61). Coculture of proximal tubule cells and podocytes under high glucose conditions led to NFAT2 activation, with downregulation of long non-coding RNA (lncRNA) NONHSAT179542.1 in podocytes, contributing to podocyte cytoskeletal damage[110]. Interestingly, in our studies of sequential tubular and glomerular injury detailed above[108], we did not find a significant increase in TGFβ or its downstream signalling molecules, although there was a small but measurable increase in interstitial fibrosis in these mice following the mild ATI.

Tubule SIRT1–podocyte claudin 1 interactions

Sirtuins exert numerous effects on cellular metabolism and are well described to decrease ageing-related tissue injury[111]. SIRT1 is a NAD^+-regulated deacetylase and in two mouse models of diabetes (a type 1 diabetes model induced by streptozotocin and the leptin receptor-deficient *db/db* mouse model of type 2 diabetes), a SIRT1

decrease in proximal tubules preceded albuminuria[112]. In vivo, conditional knockout of *Sirt1* in the proximal tubules of these diabetic mice aggravated glomerular injury with exacerbated podocyte foot process effacement and albuminuria (Fig. 3). Conversely, transgenic overexpression of *Sirt1* in the proximal tubules of the diabetic mice reduced albuminuria. Even non-diabetic mice with proximal tubule knockout of *Sirt1* had albuminuria[112]. DNA microarray analysis of microdissected glomeruli in wild type and *Sirt1*-knockout mice was used to assess gene expression patterns. Expression of claudin 1, a marker of parietal epithelial cells (PECs), was markedly decreased in diabetic streptozotocin mice (confirmed by PCR with reverse transcription (RT–PCR)). By contrast, immunogold electron microscopy showed that claudin 1 expression increased in podocytes in the diabetic mice, suggesting dedifferentiation[112]. Transgene expression of claudin 1 in podocytes (driven by the podocin promoter) induced albuminuria in non-diabetic mice and increased albuminuria in the diabetic mice. The overexpression of claudin 1 in podocytes was linked to decreased synaptopodin, a marker of differentiated podocytes. Of note, in the non-diabetic remnant kidney model, SIRT1 expression in tubules did not decrease with injury, and proximal tubular transgene expression of SIRT1 did not change the injury[112]. These results suggest that proximal tubule-derived SIRT1, by maintaining nicotinamide mononucleotide (NMN), can protect against albuminuria after diabetic injury. The possibility of retrograde passage of NMN from proximal tubules was investigated by injecting *N*-methylanthraniloyl-NMN (Mant-NMN), an autofluorescing molecule, into the renal artery of mice. At 1 h, Mant-NMN was present in the tubules and at 2 h it was present in the glomeruli. These data suggest that NMN from the proximal tubules could subsequently reach the glomeruli[112]. Complementary in vitro studies supported the possibility that proximal tubular cell release of NMN could mediate protective effects on glomerular epithelial cells[113].

Additional studies further investigated mechanisms of protection induced by NMN treatment in *db/db* mice. Short-term (2-week) treatment with NMN early in the course of diabetes development was linked to protection 14–20 weeks later, with maintained proximal tubule expression of SIRT1, blunted claudin 1 increase and decreased glomerular injury with less podocyte foot process effacement[114]. The long-lasting beneficial treatment effects were postulated to reflect epigenetic changes, with less aberrant methylation of claudin 1. Studies dissecting metabolic pathways through spatial transcriptomics and single-nucleus RNA sequencing have shed further light on the effects of NAD^+ on proximal tubules compared with podocytes after kidney injury[115]. In an Alport mouse model, in which COL4(A3) deficiency causes CKD, untreated mice had similar injury signals in proximal

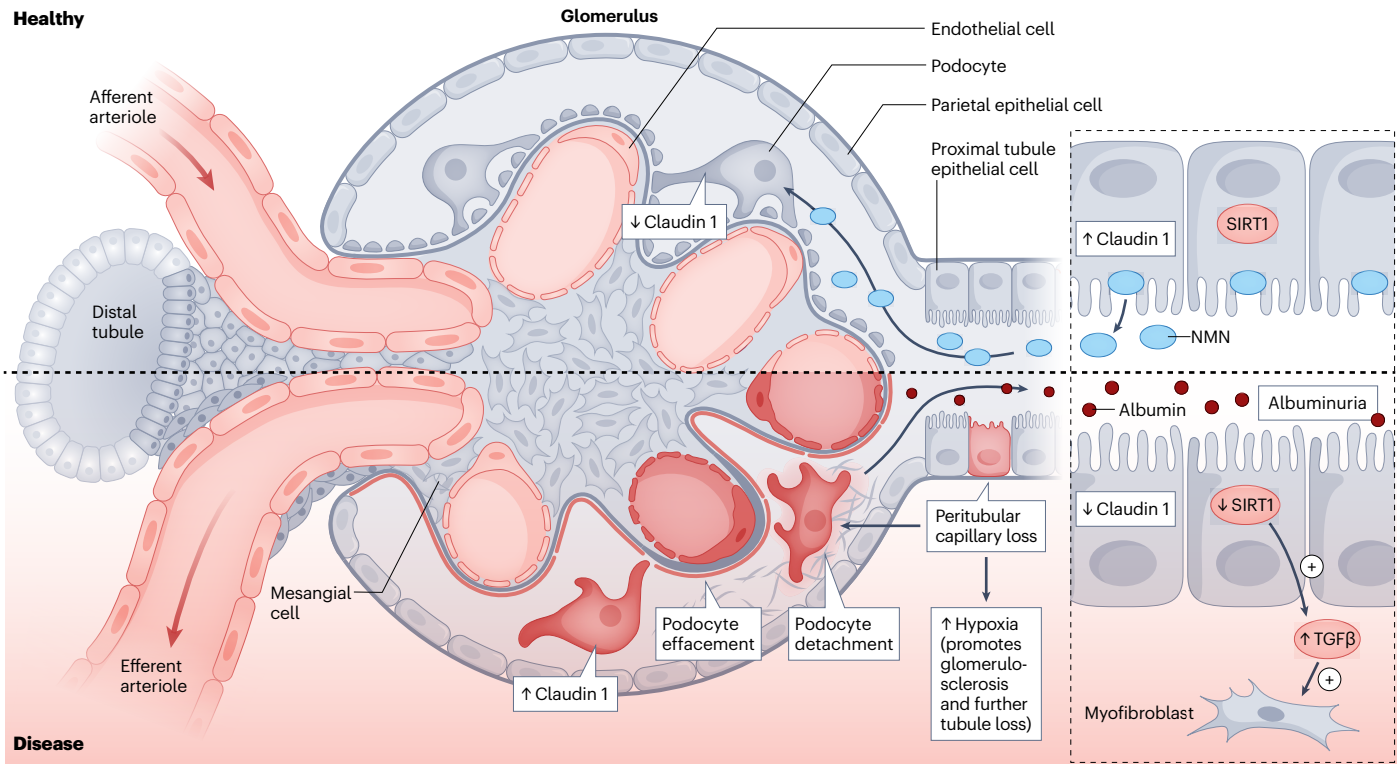

Fig. 3 | Potential mediators of tubule-induced glomerular injury. Sirtuins (SIRTs) can modulate cellular metabolism and decrease cell injury. In experimental models of diabetes, proximal tubule SIRT1 expression decreased prior to development of albuminuria, and conditional knockout of proximal tubule *Sirt1* aggravated glomerular injury and increased albuminuria in both diabetic mice and non-diabetic mice. By contrast, transgenic overexpression of *Sirt1* in the proximal tubule resulted in less albuminuria in diabetic mice. Loss of *Sirt1* was associated with decreased claudin 1 expression in parietal cells and increased expression in podocytes, suggesting podocyte dedifferentiation. These alterations in claudin 1 expression might underlie the dysregulation of glomerular function resulting from decreased proximal tubule SIRT1 expression. Accordingly, selective overexpression of claudin 1 in podocytes increased albuminuria in diabetic mice. In other studies, proximal tubular cell release of nicotinamide mononucleotide (NMN) has been proposed to affect glomerular cells. Proximal tubule-derived SIRT1 might protect against tubule-induced glomerular injury, as well as maintain proximal tubule viability and prevent the development of tubulointerstitial fibrosis, by maintaining NMN. TGFβ, transforming growth factor-β.

tubules and podocytes, with decreased NAD^+, increased fatty acid degradation and increased injury and profibrotic markers, such as increased KIM1, NGAL and osteopontin. However, treatment with nicotinamide riboside, a precursor of NAD^+, protected the mice from injury through stimulation of peroxisome proliferator-activated receptor-α, which restored impaired fatty-acid oxidation, and the expression of other metabolic and endocrine function markers in the proximal tubules, but had little effect on the signalling profiles of podocytes. These results show that tubular protective effects can indirectly have beneficial effects on glomerular injury.

Tubule–PEC interactions

The proximal tubule connection with the glomerulus allows for direct communication between tubular epithelial cells and the cells lining Bowman's capsule. The degree of tubulointerstitial fibrosis after experimental ATI correlated with the development of secondary glomerulosclerosis[116]. Some mechanisms underlying glomerular injury following ATI might result from local effects directly on the glomerulus and its response to injury. Podocytes have limited or no regenerative capacity but PECs and renin-positive cells are potential progenitor cells that might replace injured podocytes. Activated PECs express the activation marker CD44 and can migrate along Bowman's capsule, reaching glomerular tuft areas via the vascular pole or via adhesions[117], where they can produce ECM[118]. However, PECs can also express podocyte markers such as nephrin following glomerular injury, suggesting a potential contribution to podocyte regeneration[119,120]. Three types of PEC can be distinguished along Bowman's capsule: cuboidal, intermediate and flat[121]. In a focal segmental sclerosis model, cuboidal and intermediate PECs contributed to sclerotic lesions[121].

During development, PECs near the vascular pole can migrate along Bowman's capsule to the vascular stalk and reach the tuft, where they can differentiate into podocytes[122]. In mice, particularly in male mice, PECs have a proximal tubule-type phenotype and express stem cell markers, including CD133 and CD24 (refs. 123–125). Subtypes of these PECs might have varying progenitor potential. In the tuft, these PECs might contribute to sclerosis through ECM production or become podocyte-like. Tubular injury could affect the transition and migration of such progenitor cells, and thus limit or enhance the potential of glomeruli to repair after podocyte injury. Lineage tracing in mice suggested that when glomeruli become disconnected from their tubules (atubular glomeruli, see below), PECs are ablated and podocytes can migrate to line Bowman's capsule, rather than support in situ differentiation of PECs to podocyte-like cells[126]. Whether transition of PECs and/or proximal tubular cells to the glomerular tuft to become podocyte-like cells occurs in injury where glomeruli and tubules remain connected has not been proved in humans. In addition, $renin^+$ cells might also serve as progenitor cells, replacing not only podocytes but PECs and mesangial cells after injury[127,128]. Not only are $renin^+$ cells located at the juxtaglomerular apparatus, but renin-lineage cells (identified by lineage tracing in transgenic mice), which normally do not express renin, can also be found throughout the tubulointerstitium[129]. After injury, these renin-lineage cells are activated and can migrate to the glomeruli and might contribute to repair.

Tubule hypoxia leading to glomerular injury

Classically, tubular hypoxia with consequent tubulointerstitial fibrosis has been associated with scarring of the upstream glomerulus, with decreasing perfusion to the connected tubular elements. Interstitial fibrosis and tubular atrophy correlate better with CKD progression than the extent of glomerulosclerosis, perhaps because the tubules within a biopsy represent a larger number of nephrons than the relatively small glomerular sample[2,130]. Proximal tubular cells are particularly sensitive to hypoxic injury and might either repair and regenerate or undergo G2/M cell-cycle arrest with increased senescence and enhanced SASP. SASP promotes increased profibrotic and pro-inflammatory pathways that result in increased tubulointerstitial fibrosis[82].

Interstitial hypoxia is both a consequence of injury and can directly cause further injury of the surrounding tubular elements and the glomerulus. Multiple in vivo experimental models of mouse kidney injury have directly demonstrated decreased kidney pO_2, measured by microelectrodes or pimonidazole staining[131,132]. These findings were demonstrated in models of diabetic nephropathy, glomerulonephritis, polycystic kidney disease (PKD), cyclosporin toxicity and in ageing (reviewed in Palm and Nordquist[133]). Peritubular capillary loss in the hypoxic tubulointerstitium further amplifies the regional hypoxia. The so-called 'chronic hypoxia hypothesis' focused on how primary glomerular disease could decrease downstream blood flow and injure peritubular capillaries, resulting in hypoxia and fibrosis in the tubulointerstitial cells[134]. However, initial injury to the tubules with rarefaction of peritubular capillaries is also associated with progressive glomerular and tubulointerstitial scarring. When cultured tubular epithelial cells are exposed to hypoxia, they might undergo apoptosis or adopt a myofibroblast-like phenotype with increased migratory capacity and enhanced production of collagen I and α-smooth muscle cell actin[135]. In vivo, experimental evidence shows that severe tubular injury induces interstitial fibrosis, thereby aggravating hypoxia[136]. In response to this hypoxia, HIF expression increases, resulting in changes in energy metabolism and activation of angiogenesis and erythropoiesis[137–139]. Under physiological conditions, HIFα is rapidly degraded by the E3-ubiquitin ligase containing von Hippel–Lindau[140]. Under hypoxic conditions, HIFα is stabilized and can dimerize with HIFβ to form active HIF[18]. Inhibition of HIF degradation reduced oxidative stress and decreased tubulointerstitial injury in experimental models in vivo[141].

With chronic hypoxia, persistent HIF expression in tubular cells might promote profibrotic responses, as reported in diabetic nephropathy, PKD and kidney grafts[142–145], along with increased inflammation. These inflammatory responses can induce pro-mesenchymal transformation of the tubular epithelial cells and cell death[63]. Runt-related transcription factor 1 (RUNX1) derived from injured tubular epithelial cells can modify this inflammatory cascade and promote fibroblast-to-myofibroblast differentiation[146]. In an experimental model of sepsis-induced ATI, decreased endothelial progenitor cell-derived microRNA-21-5p, which targets RUNX1, was associated with upregulation of RUNX1. Increasing microRNA-21-5p in this in vivo model reduced kidney injury and systemic inflammation, while ameliorating endothelial glycocalyx damage[147]. Release of high mobility group box 1 (HMGB1) by tubules in response to hypoxic injury might also stimulate inflammatory pathways[148], and could thus potentially affect glomerular cells.

AKI can also affect the kidney via systemic effects. AKI disrupted T cell trafficking, notably in the lungs, and shifted the balance of pro- and anti-inflammatory pathway activation, promoting apoptosis and lung injury[149,150]. Altered RAAS activation after ATI can also affect glomerular injury indirectly through effects on systemic blood pressure[151].

Glomerular injury in atubular glomeruli

After ATI, mice have increased atubular glomeruli, defined as glomeruli that lack connection to their proximal tubules[108]. Atubular glomeruli are found in humans with tubulointerstitial fibrosis associated with various

diseases, including chronic pyelonephritis, ureteral obstruction, PKD and diabetic nephropathy[87,152–154], and are associated with decreased GFR and progression of glomerulosclerosis. Experimental models of kidney disease, including unilateral ureteral obstruction, 5/6 nephrectomy, PKD and ATI models, also demonstrate an increase in atubular glomeruli[87,108,155–157]. These atubular glomeruli contribute minimally to filtration and might increase the workload in the remaining connected glomeruli and, thus, promote injury[155].

In our aforementioned sequential model of ATI followed by podocyte toxin injection, we observed less glomerulosclerosis in atubular glomeruli than in connected glomeruli[109]. Possible underlying mechanisms include reduced filtration in the atubular glomeruli and less oxidative stress in podocytes. Additionally, our unpublished spatial transcriptomics data indicate that after ATI, proximal tubules can modify glomerular epithelial cells by changing local ligand–receptor pairs, with ligands originating from the proximal tubule and receptors expressed on the glomerular epithelial cells[158]. In the rat 5/6 nephrectomy model, atubular glomeruli preceded glomerulosclerosis[156]. To facilitate the study of atubular glomeruli, we developed artificial intelligence-guided methods to assess serial section whole-slide images, thus markedly decreasing the previous highly laborious task of tracking individual glomeruli three-dimensionally to assess their connectivity status[155]. These atubular glomeruli might still have tuft perfusion through the local effects of renin-secreting cells, although they contribute minimally to overall kidney GFR[87,155,156]. In the cisplatin-induced ATI model, kidney filtration function, assessed by blood urea, correlated inversely with the proportion of atubular glomeruli[152].

Conclusion

The topology of the kidney and the interconnectivity of glomerular and tubular functions indicate the importance of glomerular–tubular interactions. Although glomerular damage and alterations in glomerular function, including increased filtration barrier permeability, have been previously documented to induce changes in tubule function and structure, the underlying mechanisms are still being actively investigated. Several studies have begun to elucidate potential mediators and mechanisms of proximal tubule injury induced in proteinuric states, and a growing body of evidence suggests that primary alterations in tubule function can also lead to secondary effects on the glomerulus. Although tubule-to-glomerulus crosstalk is a newer area of investigation, several studies have identified potential factors associated with tubular injury, including epithelial cell dedifferentiation and apoptosis, as well as interstitial fibrosis, that can promote damage in all cell types of the glomerulus. Continued studies of the crosstalk between the glomerulus and the tubules in kidney injury will provide additional insights into the mechanisms underlying kidney function and dysfunction.

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References

1. Striker, G. E., Schainuck, L. I., Cutler, R. E. & Benditt, E. P. Structural-functional correlations in renal disease. I. A method for assaying and classifying histopathologic changes in renal disease. *Hum. Pathol.* **1**, 615–630 (1970).
2. Schainuck, L. I., Striker, G. E., Cutler, R. E. & Benditt, E. P. Structural-functional correlations in renal disease. II. The correlations. *Hum. Pathol.* **1**, 631–641 (1970).
3. Brenner, B. M., Goldszer, R. C. & Hostetter, T. H. Glomerular response to renal injury. *Contrib. Nephrol.* **33**, 48–66 (1982).
4. Ferenbach, D. A. & Bonventre, J. V. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. *Nat. Rev. Nephrol.* **11**, 264–276 (2015).
5. Basile, D. P. et al. Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. *J. Am. Soc. Nephrol.* **27**, 687–697 (2016).
6. Basile, D. P., Anderson, M. D. & Sutton, T. A. Pathophysiology of acute kidney injury. *Compr. Physiol.* **2**, 1303–1353 (2012).
7. Harris, R. C., Seifter, J. L. & Brenner, B. M. Adaptation of Na+-H+ exchange in renal microvillus membrane vesicles. Role of dietary protein and uninephrectomy. *J. Clin. Invest.* **74**, 1979–1987 (1984).
8. Liu, H. et al. Epigenomic and transcriptomic analyses define core cell types, genes and targetable mechanisms for kidney disease. *Nat. Genet.* **54**, 950–962 (2022).
9. Qiu, C. et al. Renal compartment-specific genetic variation analyses identify new pathways in chronic kidney disease. *Nat. Med.* **24**, 1721–1731 (2018).
10. Russo, L. M. et al. Impaired tubular uptake explains albuminuria in early diabetic nephropathy. *J. Am. Soc. Nephrol.* **20**, 489–494 (2009).
11. Haymann, J. P. et al. Characterization and localization of the neonatal Fc receptor in adult human kidney. *J. Am. Soc. Nephrol.* **11**, 632–639 (2000).
12. Nielsen, R., Christensen, E. I. & Birn, H. Megalin and cubilin in proximal tubule protein reabsorption: from experimental models to human disease. *Kidney Int.* **89**, 58–67 (2016).
13. Park, C. H. & Maack, T. Albumin absorption and catabolism by isolated perfused proximal convoluted tubules of the rabbit. *J. Clin. Invest.* **73**, 767–777 (1984).
14. Gudehithlu, K. P., Pegoraro, A. A., Dunea, G., Arruda, J. A. & Singh, A. K. Degradation of albumin by the renal proximal tubule cells and the subsequent fate of its fragments. *Kidney Int.* **65**, 2113–2122 (2004).
15. Molitoris, B. A. & Wagner, M. C. Is albumin toxic to the kidney: it depends? *Clin. J. Am. Soc. Nephrol.* **18**, 1222–1224 (2023).
16. Bedin, M. et al. Human C-terminal CUBN variants associate with chronic proteinuria and normal renal function. *J. Clin. Invest.* **130**, 335–344 (2020).
17. Molitoris, B. A., Sandoval, R. M., Yadav, S. P. S. & Wagner, M. C. Albumin uptake and processing by the proximal tubule: physiological, pathological, and therapeutic implications. *Physiol. Rev.* **102**, 1625–1667 (2022).
18. Weyer, K. et al. Abolishment of proximal tubule albumin endocytosis does not affect plasma albumin during nephrotic syndrome in mice. *Kidney Int.* **93**, 335–342 (2018).
19. Birn, H., Nielsen, R. & Weyer, K. Tubular albumin uptake: is there evidence for a quantitatively important, receptor-independent mechanism? *Kidney Int.* **104**, 1069–1073 (2023).
20. Kantarci, S. et al. Mutations in LRP2, which encodes the multiligand receptor megalin, cause Donnai-Barrow and facio-oculo-acoustico-renal syndromes. *Nat. Genet.* **39**, 957–959 (2007).
21. Charlton, J. R. et al. Beyond the tubule: pathological variants of LRP2, encoding the megalin receptor, result in glomerular loss and early progressive chronic kidney disease. *Am. J. Physiol. Renal Physiol.* **319**, F988–F999 (2020).
22. Faivre, A. et al. Spatiotemporal landscape of kidney tubular responses to glomerular proteinuria. *J. Am. Soc. Nephrol.* **35**, 854–869 (2024).
23. Langelueddecke, C. et al. Lipocalin-2 (24p3/neutrophil gelatinase-associated lipocalin (NGAL)) receptor is expressed in distal nephron and mediates protein endocytosis. *J. Biol. Chem.* **287**, 159–169 (2012).
24. Dizin, E. et al. Albuminuria induces a proinflammatory and profibrotic response in cortical collecting ducts via the 24p3 receptor. *Am. J. Physiol. Renal Physiol.* **305**, F1053–F1063 (2013).
25. Hinrichs, G. R. et al. Urokinase-type plasminogen activator contributes to amiloride-sensitive sodium retention in nephrotic range glomerular proteinuria in mice. *Acta Physiol.* **227**, e13362 (2019).
26. Svenningsen, P. et al. Plasmin in nephrotic urine activates the epithelial sodium channel. *J. Am. Soc. Nephrol.* **20**, 299–310 (2009).
27. Bohnert, B. N. et al. Urokinase-type plasminogen activator (uPA) is not essential for epithelial sodium channel (ENaC)-mediated sodium retention in experimental nephrotic syndrome. *Acta Physiol.* **227**, e13286 (2019).
28. Staehr, M. et al. Aberrant glomerular filtration of urokinase-type plasminogen activator in nephrotic syndrome leads to amiloride-sensitive plasminogen activation in urine. *Am. J. Physiol. Renal Physiol.* **309**, F235–F241 (2015).
29. Xiao, M. et al. Plasminogen deficiency does not prevent sodium retention in a genetic mouse model of experimental nephrotic syndrome. *Acta Physiol.* **231**, e13512 (2021).
30. Zoja, C., Benigni, A. & Remuzzi, G. Cellular responses to protein overload: key event in renal disease progression. *Curr. Opin. Nephrol. Hypertens.* **13**, 31–37 (2004).
31. Lidberg, K. A. et al. Serum protein exposure activates a core regulatory program driving human proximal tubule injury. *J. Am. Soc. Nephrol.* **33**, 949–965 (2022).
32. Morais, C., Westhuyzen, J., Metharom, P. & Healy, H. High molecular weight plasma proteins induce apoptosis and Fas/FasL expression in human proximal tubular cells. *Nephrol. Dial. Transpl.* **20**, 50–58 (2005).
33. Mackinnon, B. et al. Urinary transferrin, high molecular weight proteinuria and the progression of renal disease. *Clin. Nephrol.* **59**, 252–258 (2003).
34. Kalim, S. et al. Protein carbamylation and chronic kidney disease progression in the Chronic Renal Insufficiency Cohort Study. *Nephrol. Dial. Transpl.* **37**, 139–147 (2021).
35. Noels, H. et al. Post-translational modifications in kidney diseases and associated cardiovascular risk. *Nat. Rev. Nephrol.* **20**, 495–512 (2024).
36. Yadav, S. P. S. et al. Mechanism of how carbamylation reduces albumin binding to FcRn contributing to increased vascular clearance. *Am. J. Physiol. Renal Physiol.* **320**, F114–F129 (2021).
37. Figueroa, S. M. et al. Oxidized albumin as a mediator of kidney disease. *Antioxidants* **10**, 404 (2021).
38. Mishra, V. & Heath, R. J. Structural and biochemical features of human serum albumin essential for eukaryotic cell culture. *Int. J. Mol. Sci.* **22**, 8411 (2021).

39. Afshinnia, F. et al. Increased lipogenesis and impaired β-oxidation predict type 2 diabetic kidney disease progression in American Indians. *JCI Insight* **4**, e130317 (2019).
40. Arici, M., Chana, R., Lewington, A., Brown, J. & Brunskill, N. J. Stimulation of proximal tubular cell apoptosis by albumin-bound fatty acids mediated by peroxisome proliferator activated receptor-γ. *J. Am. Soc. Nephrol.* **14**, 17–27 (2003).
41. Kamijo, A. et al. Urinary free fatty acids bound to albumin aggravate tubulointerstitial damage. *Kidney Int.* **62**, 1628–1637 (2002).
42. Khan, S. et al. Kidney proximal tubule lipoapoptosis is regulated by fatty acid transporter-2 (FATP2). *J. Am. Soc. Nephrol.* **29**, 81–91 (2018).
43. Khan, S. et al. Lipotoxic disruption of NHE1 interaction with PI(4,5)P2 expedites proximal tubule apoptosis. *J. Clin. Invest.* **124**, 1057–1068 (2014).
44. Mitrofanova, A., Merscher, S. & Fornoni, A. Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease. *Nat. Rev. Nephrol.* **19**, 629–645 (2023).
45. Long, K. R., Rbaibi, Y., Gliozzi, M. L., Ren, Q. & Weisz, O. A. Differential kidney proximal tubule cell responses to protein overload by albumin and its ligands. *Am. J. Physiol. Renal Physiol.* **318**, F851–F859 (2020).
46. Sun, H. et al. Nonesterified free fatty acids enhance the inflammatory response in renal tubules by inducing extracellular ATP release. *Am. J. Physiol. Renal Physiol.* **319**, F292–F303 (2020).
47. Khan, S. et al. Fatty acid transport protein-2 regulates glycemic control and diabetic kidney disease progression. *JCI Insight* **5**, e136845 (2020).
48. Schelling, J. R. The contribution of lipotoxicity to diabetic kidney disease. *Cells* **11**, 114465 (2022).
49. Chen, Y. et al. Involvement of FATP2-mediated tubular lipid metabolic reprogramming in renal fibrogenesis. *Cell Death Dis.* **11**, 994 (2020).
50. Mori, Y. et al. KIM-1 mediates fatty acid uptake by renal tubular cells to promote progressive diabetic kidney disease. *Cell Metab.* **33**, 1042–1061.e7 (2021).
51. Kon, V., Yang, H. C., Smith, L. E., Vickers, K. C. & Linton, M. F. High-density lipoproteins in kidney disease. *Int. J. Mol. Sci.* **22**, 8201 (2021).
52. Morita, Y. et al. The role of complement in the pathogenesis of tubulointerstitial lesions in rat mesangial proliferative glomerulonephritis. *J. Am. Soc. Nephrol.* **8**, 1363–1372 (1997).
53. Nomura, A. et al. Role of complement in acute tubulointerstitial injury of rats with aminonucleoside nephrosis. *Am. J. Pathol.* **151**, 539–547 (1997).
54. Nangaku, M., Pippin, J. & Couser, W. G. Complement membrane attack complex (C5b-9) mediates interstitial disease in experimental nephrotic syndrome. *J. Am. Soc. Nephrol.* **10**, 2323–2331 (1999).
55. Rangan, G. K., Pippin, J. W., Coombes, J. D. & Couser, W. G. C5b-9 does not mediate chronic tubulointerstitial disease in the absence of proteinuria. *Kidney Int.* **67**, 492–503 (2005).
56. Rangan, G. K. C5b-9 does not mediate tubulointerstitial injury in experimental acute glomerular disease characterized by selective proteinuria. *World J. Nephrol.* **5**, 288–299 (2016).
57. Clark, E. C., Nath, K. A., Hostetter, M. K. & Hostetter, T. H. Role of ammonia in tubulointerstitial injury. *Min. Electrolyte Metab.* **16**, 315–321 (1990).
58. Worn, M. et al. Proteasuria in nephrotic syndrome-quantification and proteomic profiling. *J. Proteom.* **230**, 103981 (2021).
59. Branten, A. J., Kock-Jansen, M., Klasen, I. S. & Wetzels, J. F. Urinary excretion of complement C3d in patients with renal diseases. *Eur. J. Clin. Invest.* **33**, 449–456 (2003).
60. Timmerman, J. J. et al. Extrahepatic C6 is as effective as hepatic C6 in the generation of renal C5b-9 complexes. *Kidney Int.* **51**, 1788–1796 (1997).
61. Isaksson, G. L. et al. Urine excretion of C3dg and sC5b-9 coincide with proteinuria and development of preeclampsia in pregnant women with type-1 diabetes. *J. Hypertens.* **41**, 223–232 (2023).
62. Isaksson, G. L. et al. Proteinuria is accompanied by intratubular complement activation and apical membrane deposition of C3dg and C5b-9 in kidney transplant recipients. *Am. J. Physiol. Renal Physiol.* **322**, F150–F163 (2022).
63. Chen, S. J., Lv, L. L., Liu, B. C. & Tang, R. N. Crosstalk between tubular epithelial cells and glomerular endothelial cells in diabetic kidney disease. *Cell Prolif.* **53**, e12763 (2020).
64. Munkonda, M. N. et al. Podocyte-derived microparticles promote proximal tubule fibrotic signaling via p38 MAPK and CD36. *J. Extracell. Vesicles* **7**, 1432206 (2018).
65. Leung, J. C. K., Lai, K. N. & Tang, S. C. W. Role of mesangial-podocytic-tubular cross-talk in IgA nephropathy. *Semin. Nephrol.* **38**, 485–495 (2018).
66. Zhang, J. et al. Role of human mesangial-tubular crosstalk in secretory IgA-induced IgA nephropathy. *Kidney Blood Press. Res.* **46**, 286–297 (2021).
67. Jeon, J. S. et al. microRNA in extracellular vesicles released by damaged podocytes promote apoptosis of renal tubular epithelial cells. *Cells* **9**, 1409 (2020).
68. Rana, R. et al. Glomerular-tubular crosstalk via cold shock Y-box binding protein-1 in the kidney. *Kidney Int.* **105**, 65–83 (2024).
69. Miao, Z. et al. Single cell regulatory landscape of the mouse kidney highlights cellular differentiation programs and disease targets. *Nat. Commun.* **12**, 2277 (2021).
70. Muto, Y. et al. Single cell transcriptional and chromatin accessibility profiling redefine cellular heterogeneity in the adult human kidney. *Nat. Commun.* **12**, 2190 (2021).
71. Nolin, A. C. et al. Proteinuria causes dysfunctional autophagy in the proximal tubule. *Am. J. Physiol. Renal Physiol.* **311**, F1271–F1279 (2016).
72. Zhuang, Y. et al. Mitochondrial dysfunction confers albumin-induced NLRP3 inflammasome activation and renal tubular injury. *Am. J. Physiol. Renal Physiol.* **308**, F857–F866 (2015).
73. Doke, T. & Susztak, K. The multifaceted role of kidney tubule mitochondrial dysfunction in kidney disease development. *Trends Cell Biol.* **32**, 841–853 (2022).
74. Abbate, M., Zoja, C. & Remuzzi, G. How does proteinuria cause progressive renal damage? *J. Am. Soc. Nephrol.* **17**, 2974–2984 (2006).
75. de Seigneux, S. et al. Proteinuria increases plasma phosphate by altering its tubular handling. *J. Am. Soc. Nephrol.* **26**, 1608–1618 (2015).
76. Hu, J. et al. Hypoxia inducible factor-1α mediates the profibrotic effect of albumin in renal tubular cells. *Sci. Rep.* **7**, 15878 (2017).
77. Wilson, P. C. et al. Multimodal single cell sequencing implicates chromatin accessibility and genetic background in diabetic kidney disease progression. *Nat. Commun.* **13**, 5253 (2022).
78. Kirita, Y., Wu, H., Uchimura, K., Wilson, P. C. & Humphreys, B. D. Cell profiling of mouse acute kidney injury reveals conserved cellular responses to injury. *Proc. Natl Acad. Sci. USA* **117**, 15874–15883 (2020).
79. Dhillon, P. et al. The nuclear receptor ESRRA protects from kidney disease by coupling metabolism and differentiation. *Cell Metab.* **33**, 379–394.e8 (2021).
80. Gerhardt, L. M. S., Liu, J., Koppitch, K., Cippa, P. E. & McMahon, A. P. Single-nuclear transcriptomics reveals diversity of proximal tubule cell states in a dynamic response to acute kidney injury. *Proc. Natl Acad. Sci. USA* **118**, e2026684118 (2021).
81. Aggarwal, S. et al. SOX9 switch links regeneration to fibrosis at the single-cell level in mammalian kidneys. *Science* **383**, eadd6371 (2024).
82. Yang, L., Besschetnova, T. Y., Brooks, C. R., Shah, J. V. & Bonventre, J. V. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. *Nat. Med.* **16**, 535–543 (2010).
83. Taguchi, K. et al. Cyclin G1 induces maladaptive proximal tubule cell dedifferentiation and renal fibrosis through CDK5 activation. *J. Clin. Invest* **132**, e158096 (2022).
84. Coca, S. G., Singanamala, S. & Parikh, C. R. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int.* **81**, 442–448 (2012).
85. Chawla, L. S., Eggers, P. W., Star, R. A. & Kimmel, P. L. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N. Engl. J. Med.* **371**, 58–66 (2014).
86. Palant, C. E., Amdur, R. L. & Chawla, L. S. Long-term consequences of acute kidney injury in the perioperative setting. *Curr. Opin. Anaesthesiol.* **30**, 100–104 (2017).
87. Wang, J., Zhong, J., Yang, H. C. & Fogo, A. B. Cross talk from tubules to glomeruli. *Toxicol. Pathol.* **46**, 944–948 (2018).
88. Jones, J. et al. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am. J. Kidney Dis.* **60**, 402–408 (2012).
89. Harris, R. C. & Zhang, M. Z. Cyclooxygenase metabolites in the kidney. *Compr. Physiol.* **1**, 1729–1758 (2011).
90. Capasso, G. A new cross-talk pathway between the renal tubule and its own glomerulus. *Kidney Int.* **71**, 1087–1089 (2007).
91. Sen, T. & Heerspink, H. J. L. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. *Cell Metab.* **33**, 732–739 (2021).
92. Tuttle, K. R. Digging deep into cells to find mechanisms of kidney protection by SGLT2 inhibitors. *J. Clin. Invest.* **133**, e167700 (2023).
93. Nishiyama, A. & Kitada, K. Possible renoprotective mechanisms of SGLT2 inhibitors. *Front. Med.* **10**, 1115413 (2023).
94. Billing, A. M. et al. Metabolic communication by SGLT2 inhibition. *Circulation* **149**, 860–884 (2024).
95. Albalawy, W. N. et al. SGLT2-independent effects of canagliflozin on NHE3 and mitochondrial complex I activity inhibit proximal tubule fluid transport and albumin uptake. *Am. J. Physiol. Renal Physiol.* **326**, F1041–F1053 (2024).
96. Zhang, Y., Thai, K., Kepecs, D. M. & Gilbert, R. E. Sodium-glucose linked cotransporter-2 inhibition does not attenuate disease progression in the rat remnant kidney model of chronic kidney disease. *PLoS ONE* **11**, e0144640 (2016).
97. Zhu, Z. et al. Finerenone added to RAS/SGLT2 blockade for CKD in Alport syndrome. results of a randomized controlled trial with *Col4a3*$^{-/-}$ Mice. *J. Am. Soc. Nephrol.* **34**, 1513–1520 (2023).
98. Schaub, J. A. et al. SGLT2 inhibitors mitigate kidney tubular metabolic and mTORC1 perturbations in youth-onset type 2 diabetes. *J. Clin. Invest.* **133**, e164486 (2023).
99. Inoki, K. et al. mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. *J. Clin. Invest.* **121**, 2181–2196 (2011).
100. Godel, M. et al. Role of mTOR in podocyte function and diabetic nephropathy in humans and mice. *J. Clin. Invest.* **121**, 2197–2209 (2011).
101. Packer, M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation* **146**, 1383–1405 (2022).
102. Haase, V. H. Regulation of erythropoiesis by hypoxia-inducible factors. *Blood Rev.* **27**, 41–53 (2013).
103. Grgic, I. et al. Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. *Kidney Int.* **82**, 172–183 (2012).
104. Gao, L. et al. Restoration of E-cadherin by PPBICA protects against cisplatin-induced acute kidney injury by attenuating inflammation and programmed cell death. *Lab. Invest.* **98**, 911–923 (2018).
105. Xiong, C. et al. Pharmacological inhibition of Src kinase protects against acute kidney injury in a murine model of renal ischemia/reperfusion. *Oncotarget* **8**, 31238–31253 (2017).
106. Tan, R. J. et al. Tubular injury triggers podocyte dysfunction by β-catenin-driven release of MMP-7. *JCI Insight* **4**, e122399 (2019).
107. Ma, Y. et al. Paracrine effects of renal proximal tubular epithelial cells on podocyte injury under hypoxic conditions are mediated by arginase-II and TGF-β1. *Int J. Mol. Sci.* **24**, 3587 (2023).

108. Lim, B. J. et al. Tubulointerstitial fibrosis can sensitize the kidney to subsequent glomerular injury. *Kidney Int.* **92**, 1395–1403 (2017).
109. Zou, J. et al. Stabilization of hypoxia-inducible factor ameliorates glomerular injury sensitization after tubulointerstitial injury. *Kidney Int.* **99**, 620–631 (2021).
110. Xu, C. et al. Renal tubular Bim mediates the tubule-podocyte crosstalk via NFAT2 to induce podocyte cytoskeletal dysfunction. *Theranostics* **10**, 6806–6824 (2020).
111. Han, X. et al. Targeting Sirtuin1 to treat aging-related tissue fibrosis: from prevention to therapy. *Pharmacol. Ther.* **229**, 107983 (2022).
112. Hasegawa, K. et al. Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes. *Nat. Med.* **19**, 1496–1504 (2013).
113. Hasegawa, K. et al. Communication from tubular epithelial cells to podocytes through sirt1 and nicotinic acid metabolism. *Curr. Hypertens. Rev.* **12**, 95–104 (2016).
114. Yasuda, I. et al. Pre-emptive short-term nicotinamide mononucleotide treatment in a mouse model of diabetic nephropathy. *J. Am. Soc. Nephrol.* **32**, 1355–1370 (2021).
115. Jones, B. A. et al. Nicotinamide riboside activates renal metabolism and protects the kidney in a model of Alport syndrome. Preprint at *bioRxiv* https://doi.org/10.1101/2024.02.26.580911 (2024).
116. Bonventre, J. V. Primary proximal tubule injury leads to epithelial cell cycle arrest, fibrosis, vascular rarefaction, and glomerulosclerosis. *Kidney Int. Suppl.* **4**, 39–44 (2014).
117. Lasagni, L. & Romagnani, P. Glomerular epithelial stem cells: the good, the bad, and the ugly. *J. Am. Soc. Nephrol.* **21**, 1612–1619 (2010).
118. Smeets, B. et al. Parietal epithelial cells participate in the formation of sclerotic lesions in focal segmental glomerulosclerosis. *J. Am. Soc. Nephrol.* **22**, 1262–1274 (2011).
119. Kaverina, N. V. et al. Dual lineage tracing shows that glomerular parietal epithelial cells can transdifferentiate toward the adult podocyte fate. *Kidney Int.* **96**, 597–611 (2019).
120. Shankland, S. J., Pippin, J. W. & Duffield, J. S. Progenitor cells and podocyte regeneration. *Semin. Nephrol.* **34**, 418–428 (2014).
121. Kuppe, C. et al. Novel parietal epithelial cell subpopulations contribute to focal segmental glomerulosclerosis and glomerular tip lesions. *Kidney Int.* **96**, 80–93 (2019).
122. Appel, D. et al. Recruitment of podocytes from glomerular parietal epithelial cells. *J. Am. Soc. Nephrol.* **20**, 333–343 (2009).
123. Berger, K. & Moeller, M. J. Mechanisms of epithelial repair and regeneration after acute kidney injury. *Semin. Nephrol.* **34**, 394–403 (2014).
124. Angelotti, M. L. et al. Characterization of renal progenitors committed toward tubular lineage and their regenerative potential in renal tubular injury. *Stem Cell* **30**, 1714–1725 (2012).
125. Ronconi, E. et al. Regeneration of glomerular podocytes by human renal progenitors. *J. Am. Soc. Nephrol.* **20**, 322–332 (2009).
126. Schulte, K. et al. Origin of parietal podocytes in atubular glomeruli mapped by lineage tracing. *J. Am. Soc. Nephrol.* **25**, 129–141 (2014).
127. Pippin, J. W. et al. Cells of renin lineage are progenitors of podocytes and parietal epithelial cells in experimental glomerular disease. *Am. J. Pathol.* **183**, 542–557 (2013).
128. Kaverina, N. V. et al. Tracking the stochastic fate of cells of the renin lineage after podocyte depletion using multicolor reporters and intravital imaging. *PLoS ONE* **12**, e0173891 (2017).
129. Martinez, M. F. et al. Super-enhancers maintain renin-expressing cell identity and memory to preserve multi-system homeostasis. *J. Clin. Invest.* **128**, 4787–4803 (2018).
130. Risdon, R. A., Sloper, J. C. & De Wardener, H. E. Relationship between renal function and histological changes found in renal-biopsy specimens from patients with persistent glomerular nephritis. *Lancet* **2**, 363–366 (1968).
131. Welch, W. J., Baumgartl, H., Lubbers, D. & Wilcox, C. S. Nephron pO_2 and renal oxygen usage in the hypertensive rat kidney. *Kidney Int.* **59**, 230–237 (2001).
132. Rosenberger, C., Rosen, S., Paliege, A. & Heyman, S. N. Pimonidazole adduct immunohistochemistry in the rat kidney: detection of tissue hypoxia. *Methods Mol. Biol.* **466**, 161–174 (2009).
133. Palm, F. & Nordquist, L. Renal oxidative stress, oxygenation, and hypertension. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **301**, R1229–R1241 (2011).
134. Fine, L. G., Orphanides, C. & Norman, J. T. Progressive renal disease: the chronic hypoxia hypothesis. *Kidney Int. Suppl.* **65**, S74–S78 (1998).
135. Manotham, K. et al. Transdifferentiation of cultured tubular cells induced by hypoxia. *Kidney Int.* **65**, 871–880 (2004).
136. Mimura, I. & Nangaku, M. The suffocating kidney: tubulointerstitial hypoxia in end-stage renal disease. *Nat. Rev. Nephrol.* **6**, 667–678 (2010).
137. Haase, V. H. Hypoxia-inducible factors in the kidney. *Am. J. Physiol. Renal Physiol.* **291**, F271–F281 (2006).
138. Haase, V. H. Pathophysiological consequences of HIF activation: HIF as a modulator of fibrosis. *Ann. N. Y. Acad. Sci.* **1177**, 57–65 (2009).
139. Sugahara, M., Tanaka, T. & Nangaku, M. Hypoxia-inducible factor and oxygen biology in the kidney. *Kidney360* **1**, 1021–1031 (2020).
140. Kaelin, W. G. Jr. & Ratcliffe, P. J. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol. Cell* **30**, 393–402 (2008).
141. Nordquist, L. et al. Activation of hypoxia-inducible factors prevents diabetic nephropathy. *J. Am. Soc. Nephrol.* **26**, 328–338 (2015).
142. Bernhardt, W. M. et al. Involvement of hypoxia-inducible transcription factors in polycystic kidney disease. *Am. J. Pathol.* **170**, 830–842 (2007).
143. Higgins, D. F. et al. Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition. *J. Clin. Invest.* **117**, 3810–3820 (2007).
144. Higgins, D. F., Kimura, K., Iwano, M. & Haase, V. H. Hypoxia-inducible factor signaling in the development of tissue fibrosis. *Cell Cycle* **7**, 1128–1132 (2008).
145. Rosenberger, C. et al. Immunohistochemical detection of hypoxia-inducible factor-1α in human renal allograft biopsies. *J. Am. Soc. Nephrol.* **18**, 343–351 (2007).
146. Li, Z. et al. Chromatin-accessibility estimation from single-cell ATAC-seq data with scOpen. *Nat. Commun.* **12**, 6386 (2021).
147. Zhang, Y. et al. Endothelial progenitor cells-derived exosomal microRNA-21-5p alleviates sepsis-induced acute kidney injury by inhibiting RUNX1 expression. *Cell Death Dis.* **12**, 335 (2021).
148. Chen, Q., Guan, X., Zuo, X., Wang, J. & Yin, W. The role of high mobility group box 1 (HMGB1) in the pathogenesis of kidney diseases. *Acta Pharm. Sin. B* **6**, 183–188 (2016).
149. Grigoryev, D. N. et al. The local and systemic inflammatory transcriptome after acute kidney injury. *J. Am. Soc. Nephrol.* **19**, 547–558 (2008).
150. Lie, M. L. et al. Lung T lymphocyte trafficking and activation during ischemic acute kidney injury. *J. Immunol.* **189**, 2843–2851 (2012).
151. Ba Aqeel, S. H., Sanchez, A. & Batlle, D. Angiotensinogen as a biomarker of acute kidney injury. *Clin. Kidney J.* **10**, 759–768 (2017).
152. Marcussen, N. Atubular glomeruli in cisplatin-induced chronic interstitial nephropathy. An experimental stereological investigation. *APMIS* **98**, 1087–1097 (1990).
153. Marcussen, N. & Olsen, T. S. Atubular glomeruli in patients with chronic pyelonephritis. *Lab. Invest.* **62**, 467–473 (1990).
154. Najafian, B., Kim, Y., Crosson, J. T. & Mauer, M. Atubular glomeruli and glomerulotubular junction abnormalities in diabetic nephropathy. *J. Am. Soc. Nephrol.* **14**, 908–917 (2003).
155. Forbes, M. S., Thornhill, B. A. & Chevalier, R. L. Proximal tubular injury and rapid formation of atubular glomeruli in mice with unilateral ureteral obstruction: a new look at an old model. *Am. J. Physiol. Renal Physiol.* **301**, F110–F117 (2011).
156. Gandhi, M., Olson, J. L. & Meyer, T. W. Contribution of tubular injury to loss of remnant kidney function. *Kidney Int.* **54**, 1157–1165 (1998).
157. Tanner, G. A., Gretz, N., Connors, B. A., Evan, A. P. & Steinhausen, M. Role of obstruction in autosomal dominant polycystic kidney disease in rats. *Kidney Int.* **50**, 873–886 (1996).
158. Yang, H. C. et al. Spatial transcriptomic analysis reveals altered gene expression in glomerular parietal epithelial cells following tubular injury. *ASN Kidney Week* **34**, 315 (2023).

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